Diabetes Increases Atrophy and Vascular Lesions on Brain MRI in Patients With Symptomatic Arterial Disease

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Background and Purpose—Diabetes type 2 (DM2) is associated with accelerated cognitive decline and structural brain abnormalities. Macrovascular disease has been described as a determinant for brain MRI changes in DM2, but little is known about the involvement of other DM2-related factors.

Methods—Brain MRI was performed in 1043 participants (151 DM2) with symptomatic arterial disease. Brain volumes were obtained through automated segmentation.

Results—Patients with arterial disease and DM2 had more global and subcortical brain atrophy (−1.20% brain/intracranial volume [95%CI −1.58 to −0.82], P<0.0005 and 0.20% ventricular/intracranial volume [0.05 to 0.34], P<0.01), larger WMH volumes (0.22 logtransformed volume [0.07 to 0.38], P<0.005), and more lacunar infarcts (OR 1.75 [1.13 to 2.69], P<0.01) than identical patients without DM2. In patients with DM2, high glucose levels (−0.12% per mmol/L [−0.23 to −0.01], P<0.05) and diabetes duration (−0.05% per year [−0.10 to −0.001], P<0.05) were associated with global brain atrophy.

Conclusion—In patients with symptomatic arterial disease, DM2 has an added detrimental effect on the brain. In patients with DM2, hyperglycemia and diabetes duration contribute to brain atrophy. (Stroke. 2008;39:1600-1603.)

Key Words: brain imaging ■ diabetes mellitus type 2 ■ cardiovascular disease ■ cognition

Diabetes mellitus type 2 (DM2) is associated with accelerated cognitive decline and an increased risk of dementia,1 and with structural brain abnormalities, such as atrophy, white matter hyperintensities (WMH), and lacunar infarcts.2 In the general population, cardiovascular risk factors and macrovascular disease are independent risk factors for brain MRI abnormalities,3–5 but this has not been studied extensively in patients with DM2. Macrovascular disease has been suggested as the principle determinant of brain changes in DM2.6 However, the involvement of other DM2-related factors, such as hyperglycemia and hyperinsulinemia, is still unknown.

The present study examined the association between DM2 and brain MRI abnormalities in patients with symptomatic arterial disease, to determine the effect of DM2 on top of vascular disease. Secondly, we determined factors that were associated with brain MRI changes in the group of patients with DM2.

Methods

Patients were participants of the SMART-study, a prospective cohort study aimed to investigate Secondary Manifestations of Arterial Disease.7 Brain MRI was performed between May 2001 and December 2005 in all patients with symptomatic arterial disease (cerebrovascular, coronary, or peripheral artery disease). A detailed description of the study was published previously.7

Subject Characteristics

DM2 was defined as the use of glucose-lowering medication or a history of DM2. Diabetes duration was based on a standardized interview. Patients with DM1 were excluded. Height, weight, waist and hip circumference, and blood pressure were measured according to a standardized protocol. Serum levels of glucose, insulin, total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides were assessed in a fasting venous blood sample. In patients not treated with insulin, the “homeostasis model assessment of insulin resistance” (HOMA-IR) was used as a measure of insulin resistance (fasting glucose×fasting insulin/22.5). In an early morning urine sample, microalbuminuria was defined as an albumin to creatinine ratio above 3.

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1600
MR Imaging

Brain MRI was performed on a 1.5T Philips Gyroscan (Philips Medical Systems). The protocol contained transaxial T2-weighted (TR 2200 ms/TE 100 ms), T1-weighted (TR 234 ms/TE 2 ms), inversion recovery (IR; TR 2900 ms/TE 22 ms), and FLAIR (TR 6000 ms/TI 2000 ms/TE 100 ms) scans, performed with 38 slices of 4-mm thickness without slice gap, covering the entire brain, FOV 230/H11005230 mm and 256/H11005256 matrix. Volumetric assessment of the brain was performed with an automated segmentation method. Estimates of global and subcortical brain atrophy were made by expressing brain tissue and ventricular volumes as percentages of total intracranial volume (ICV), resulting in the brain parenchymal fraction (BPF) and ventricular fraction (VF). Normalized WMH volumes (nWMH) were calculated by dividing the patient’s WMH volume by the ratio of the patient’s ICV to the mean ICV of the population. When present, cerebral infarcts were manually segmented and distinguished into large (cortical or subcortical) and lacunar infarcts.

Statistical Analysis

Between group differences in MRI measures were analyzed with general linear models (expressed as mean differences) or logistic regression analysis (OR), adjusted for age, gender, and additionally for other potential determinants. Within the DM2 group, relations between brain MRI measures and clinical determinants were analyzed with linear regression (regression-coefficient B) or logistic regression (OR) analysis, adjusted for age and gender. nWMH volumes (in mL) were natural logtransformed to obtain a normally distributed variable. All models with atrophy as dependent variable were adjusted for infarct volume.

Results

Segmentation data were available for 1044 of the 1309 patients. In 1 patient no information was present on diabetic status or medication. Patient characteristics are presented in Table 1.

Vascular patients with DM2 had a smaller BPF, larger VF, and more WMH and (silent) lacunar infarcts than vascular patients without DM2 (Table 2). They did not differ in number of large infarcts. The associations found between DM2 and MRI abnormalities persisted after adjustment for age, gender, vascular risk factors, and cerebrovascular disease. Exclusion of patients with large infarcts did not affect the differences in brain atrophy between the groups (BPF: P<0.0005, VF: P<0.05).

In patients with DM2, determinants for decreased BPF were fasting serum glucose levels and diabetes duration (Table 3). We found no DM2-specific determinants that were associated with VF. Exclusion of patients with large infarcts did not affect the association with BPF (fasting glucose:

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM2 (n=151)</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Male, %</td>
</tr>
<tr>
<td>Vascular risk factors</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Waist, cm</td>
</tr>
<tr>
<td>Hypertension, %</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
</tr>
<tr>
<td>Smoking, %</td>
</tr>
<tr>
<td>Diabetes-specific factors</td>
</tr>
<tr>
<td>Fasting serum glucose, mmol/l</td>
</tr>
<tr>
<td>Mean diabetes duration, y</td>
</tr>
<tr>
<td>Antidiabetic-medication, %</td>
</tr>
<tr>
<td>Use of insulin, %</td>
</tr>
<tr>
<td>HOMA-IR</td>
</tr>
<tr>
<td>Macrovacular disease</td>
</tr>
<tr>
<td>Cerebrovascular disease, %</td>
</tr>
<tr>
<td>Peripheral artery disease, %</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
</tr>
<tr>
<td>Microvascular disease</td>
</tr>
<tr>
<td>Microalbuminuria, %</td>
</tr>
</tbody>
</table>

Data are means (SD), percentages, or medians (interquartile range). NA indicates not applicable. Hypertension was defined as a mean systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥95 mm Hg, or use of antihypertensive medication. Hyperlipidemia was defined as a total cholesterol level ≥5.0 mmol/L, a LDL level ≥3.2 mmol/L, or use of lipid lowering drugs.
Table 2. Atrophy and Vascular Lesions on Brain MRI in Vascular Patients With and Without Diabetes

<table>
<thead>
<tr>
<th>Model</th>
<th>Diabetes Type 2 (n=151)</th>
<th>No Diabetes Type 2 (n=892)</th>
<th>Mean Difference or OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global atrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>77.2 (SEM 0.25)</td>
<td>79.1 (SEM 0.10)</td>
<td>−1.89 (−2.41 to −1.36)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Model 2</td>
<td>77.9</td>
<td>79.0</td>
<td>−1.20 (−1.58 to −0.82)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Model 3</td>
<td>77.8</td>
<td>79.0</td>
<td>−1.16 (−1.54 to −0.77)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Subcortical atrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>2.41 (SEM 0.08)</td>
<td>2.04 (SEM 0.03)</td>
<td>0.37 (0.20 to 0.53)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Model 2</td>
<td>2.26</td>
<td>2.06</td>
<td>0.20 (0.05 to 0.34)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Model 3</td>
<td>2.25</td>
<td>2.07</td>
<td>0.19 (0.03 to 0.34)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>White matter hyperintensities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.00 (SEM 0.08)</td>
<td>0.61 (SEM 0.03)</td>
<td>0.39 (0.21 to 0.57)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.86</td>
<td>0.64</td>
<td>0.22 (0.07 to 0.38)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.86</td>
<td>0.63</td>
<td>0.23 (0.07 to 0.39)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lacunar Infarcts</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>36 (24)</td>
<td>119 (13)</td>
<td>NA</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.75 (1.13 to 2.69)</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>1.73 (1.04 to 2.87)</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Large Infarcts</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>20 (13)</td>
<td>90 (10)</td>
<td>NA</td>
<td>0.3</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.25 (0.74 to 2.11)</td>
<td></td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Model 3*</td>
<td>1.23 (0.71 to 2.14)</td>
<td></td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

Model 1: unadjusted.  
Model 2: adjusted for age and gender.  
Model 3: as model 1, additionally adjusted for presence of hypertension, BMI, waist, total cholesterol, smoking, and cerebrovascular disease. *Large infarcts were not adjusted for presence of cerebrovascular disease. (Global and subcortical atrophy were additionally adjusted for infarct volume, if present).  
LN indicates natural logtransformed.

P<0.05, DM2 duration: P<0.05). DM2 patients with cerebrovascular disease had significantly more WMH and (silent) lacunar infarcts, compared to patients who had manifestations of arterial disease elsewhere. Current smoking was associated with lacunar infarcts. No diabetes-specific factors were related to vascular lesions.

Discussion

In the present study, DM2 had an independent detrimental effect on the brain on top of macrovascular disease. DM2 is a complex disease with various metabolic and vascular comorbidities. Knowledge of the determinants for cerebral damage in DM2 patients might identify those at higher risk for accelerated cognitive decline. Although macrovascular disease has been described as a principle determinant for brain MRI abnormalities, we demonstrated that within a group of patients with arterial disease and DM2, diabetes-specific factors such as fasting serum glucose levels and duration of hyperglycemia contributed to the extent of brain atrophy.

Table 3. Determinants for Brain MRI Measures in Patients With Diabetes

<table>
<thead>
<tr>
<th>Vascular risk factors</th>
<th>Global Atrophy BPF (%)</th>
<th>Subcortical Atrophy VF (%)</th>
<th>White Matter Hyperintensities</th>
<th>Lacunar Infarcts (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>P Value</td>
<td>Logtransformed Volume (LN ml)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>P Value</td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>P Value</td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>P Value</td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.01 (−0.09 to 0.11)</td>
<td>0.9</td>
<td>−0.02 (−0.07 to 0.02)</td>
<td>0.3</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>−0.01 (−0.04 to 0.03)</td>
<td>0.8</td>
<td>−0.01 (−0.03 to 0.01)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension, yes/no</td>
<td>−0.63 (−1.40 to 0.13)</td>
<td>0.1</td>
<td>0.13 (−0.20 to 0.48)</td>
<td>0.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>−0.01 (−0.03 to 0.01)</td>
<td>0.3</td>
<td>0.01 (−0.002 to 0.01)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>−0.03 (−0.06 to 0.01)</td>
<td>0.1</td>
<td>0.004 (−0.01 to 0.02)</td>
<td>0.6</td>
</tr>
<tr>
<td>Hyperlipidemia, yes/no</td>
<td>−0.71 (−1.53 to 0.12)</td>
<td>0.09</td>
<td>0.06 (−0.32 to 0.43)</td>
<td>0.8</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>−0.24 (−0.64 to 0.16)</td>
<td>0.2</td>
<td>−0.06 (−0.25 to 0.09)</td>
<td>0.4</td>
</tr>
<tr>
<td>Smoking, yes/no</td>
<td>−0.48 (−1.34 to 0.39)</td>
<td>0.3</td>
<td>0.19 (−0.19 to 0.56)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

(Continued)
We defined diabetes as a known history of DM2 or treated DM2. Therefore, a considerable proportion of patients in the non-DM2 group may have undetected DM2, becoming apparent only by performing an oral glucose tolerance test. Therefore, our results may imply that a relative long duration of DM2 will lead to brain atrophy. Some strengths of this study are the use of an accurate automated brain segmentation method enabling volumetric assessment of the brain, the large number of patients that underwent brain MRI, and the relatively large number of patients with DM2. Because we studied the effect of DM2 on brain changes in patients with symptomatic arterial disease, it should be noted that our findings may not be representative for the population of DM2 patients as a whole.

We conclude that in patients with symptomatic arterial disease, DM2 has an added detrimental effect on the brain, reflected in more atrophy, WMH, and infarcts. Hyperglycemia and diabetes duration are the main determinants for brain atrophy in patients with arterial disease and DM2.

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Disclosures
None.

References
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